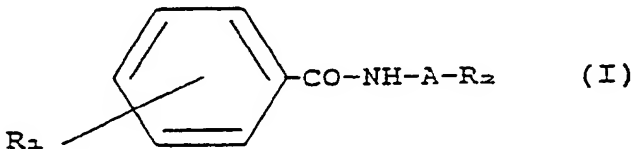




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(21) International Application Number: PCT/EP93/00326 (22) International Filing Date: 11 February 1993 (11.02.93) (30) Priority data: TO92A000114 13 February 1992 (13.02.92) IT (71) Applicant (for all designated States except US): ROTTA RE- SEARCH LABORATORIUM S.P.A. [IT/IT]; Via Valo- sa di Sopra, 7/9, I-20052 Monza (IT). (72) Inventors; and (75) Inventors/Applicants (for US only) : MAKOVEC, Francesco [IT/IT]; Via Boito, 72, I-20052 Monza (IT). PERIS, Wal- ter [IT/IT]; Piazza Spotorno, 3, I-20159 Milano (IT). ROVATI, Lucio, Claudio [IT/IT]; Via Cagni, 8, I-20052 Monza (IT). ROVATI, Luigi, Angelo [IT/IT]; Via Valosa di Sopra, 28, I-20052 Monza (IT).		(74) Agents: RAMBELLI, Paolo et al.; Jacobacci-Casetta & Perani S.p.A., Via Alfieri, 17, I-10121 Torino (IT). (81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: NOVEL BISTETRAZOL DERIVATIVES HAVING AN ANTIALLERGIC AND CYTOPROTECTIVE ACTIVI- TY		
<div style="text-align: center;">  <p style="text-align: right;">(I)</p> </div>		
(57) Abstract <p>Pharmaceutically active N-phenyl-benzamide and N-pyridinyl-benzamide compounds having formula (I) in which A is the benzene ring or the pyridine ring and R₁ and R₂ both represent the group (1H tetrazol-5-yl), and in which, if R₁ is in the ortho or meta position in the benzamide group, R₂ is in the ortho, meta or para position in ring A, whereas if R₁ is in the para position in the benzamide group, R₂ can be in the ortho or meta position in ring A, and their pharmaceutically acceptable salts.</p>		

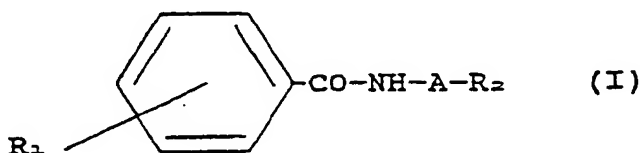
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Novel bistetrazol derivatives having an anti-allergic and cytoprotective activity

The present invention relates to novel N-phenylbenzamide and N-pyridine-benzamide derivatives represented by the following general formula:



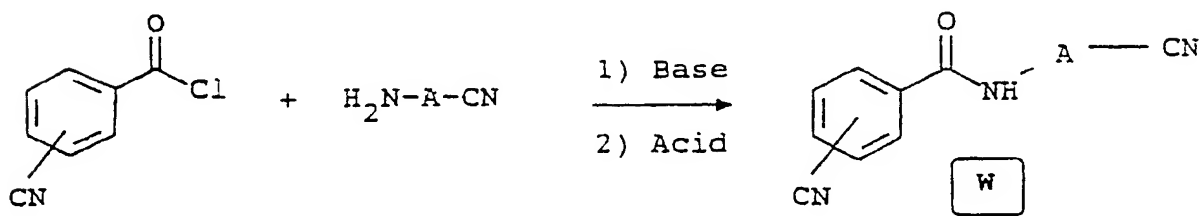
in which A is the benzene ring or the pyridine ring and R₁ and R₂ both represent the group (1H-tetrazol-5-yl), and in which, if R₁ is in the ortho or meta position in the benzamide group, R₂ is in the ortho, meta or para position in ring A, whilst, if R₁ is in the para position in the benzamide group, R₂ can be in the ortho or meta position in ring A, and their pharmaceutically acceptable salts. These compounds have proved to have remarkable pharmacological effects with respect to mammals, one of which is their powerful inhibiting activity on the release of chemical agents causing allergic or immunological reactions. A further property consists in their equally powerful protective and healing activity with respect to the epithelial mucose membranes. A further activity is their antisecretion activity with respect to various secretion stimulants, such as histamine, carbachol and pentagastrine.

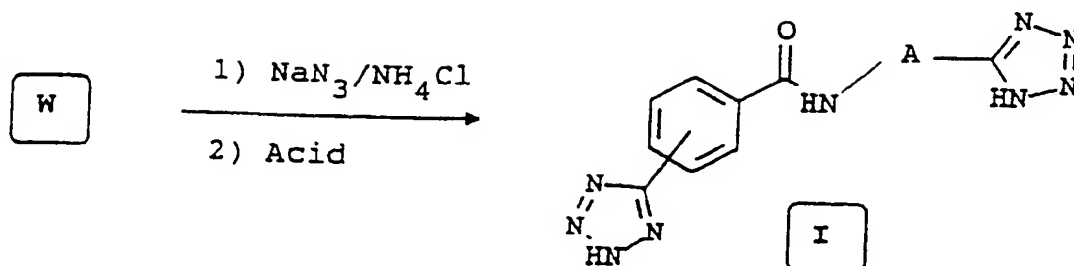
The aforementioned compounds can thus be used advantageously in the treatment of various human diseases, such as those which are due to hypersensitivity to allergens, such as bronchial asthma, for example, allergic rhinitis or conjunctivitis, or other pathological conditions of further organs or areas, or in the treatment of diseases of the digestive system, such as those deriving from gastric secretion disorders or mucosal lesions, i.e. peptic and gastro-duodenal ulcers, colitis, or in allergies and intolerance in the alimentary system.

The process for preparing N-phenyl and N-pyridinyl-benzamido-bis-tetrazol derivatives according to the invention is characterized by a two-stage synthesis, illustrated in diagram 1.

Diagram 1: Process for synthesising the compounds claimed according to the invention.

Step 1



Step 2

In practice, aniline or aminopyridine optionally substituted in R_2 with the cyano group is made to react with the stoichiometric amount of benzoyl chloride optionally substituted in R_1 with the cyano group dissolved in a polar solvent, preferably tetrahydrofuran, in the presence of a tertiary base such as triethylamine, for example, which acts as a hydrochloric acid acceptor, at a temperature of between 0 and 20° C, preferably approximately 10° C, for an amount of time which can vary from approximately one hour to twenty-four hours; in general, the reaction is considered to be complete after 12 hours. The solvent evaporates under vacuum, the residue is taken up with water, filtered, washed until it is neutral and dried. The compound is then converted into the bis-tetrazol derivative as a result of being reacted in the hot state with sodium azide and ammonium chloride in a high-boiling point solvent, preferably dimethylformamide, at a temperature of between 60° and 140° C (preferably 100 ° C). The reaction time varies between 8 and 36 hours and on average 24 hours are sufficient for the

reaction to be completed. At the end of the reaction, the reaction mixture is diluted with water and acidified. The precipitate is filtered, washed to neutralize it and optionally crystallized. The following examples are given to illustrate better the invention.

Example 1

N-(4-cyano)-phenyl-3-cyano-benzamide (compound 1)

13.1 g (0.13 moles) triethylamine are added to a solution of 14.2 g (0.12 moles) 4-aminobenzonitrile in 100 ml tetrahydrofuran and then, with the temperature being maintained at approximately 5° C, 20 g (0.12 moles) 3-cyano-benzoyl chloride are added dropwise. The mixture is left to react for 12 hours under agitation. The solvent is evaporated, the residue is taken up with water and the resultant precipitate is filtered. It is washed with dilute HCl, a 10% bicarbonate solution and again with water.

Obtained: 26.1 g. Formula: $C_{15}H_9N_3O$. Yield 88%

TLC on silica gel (benzene acetic acid Met: OH:6/1/1):Rf 0.53

Melting point: 220° C.

Example 2

N-[(4-cyano)-pyridine-2-yl]-3-cyanobenzamide
(compound 2)

13.1 g (0.13 moles) triethylamine are added to a solution of 14.3 g (0.12 moles) 2-amino-5-cyanopyridine dissolved in 150 ml tetrahydrofurane, and then, with the temperature being maintained at approximately 5° C, 20 g (0.12 moles) 3-cyanobenzoyl chloride are added dropwise. The mixture is left to react for 12 hours under agitation. The solvent is evaporated, the residue is taken up with water and the resultant precipitate is filtered. It is washed with a little cold dilute HCl, a 10% bicarbonate solution and once again with water.

Obtained: 21.2 g. Formula: $C_{14}H_8N_4O$. Yield: 71%.

TLC on silica gel (benzene acetic acid Met:

OH:6/1/1): Rf 0.55

Melting point: 187-189° C.

All the compounds of formula "W" illustrated by the general synthesis diagram are synthesised in accordance with the above processes.

Example 3

N-[4-(1H-tetrazol-5-yl)]-phenyl-3-(1H-tetrazol-5-yl) benzamide (compound 3)

21 g (0.32 moles) sodium azide and 18.7 g (0.35 moles) ammonium chloride are added to a suspension of 20 g (0.08 moles) N-(4-cyano)-phenyl-3-cyano-benzamide (compound 1) in 300 ml of dimethylformamide. The mixture is left to react at 100° C under agitation for 24 hours. It is diluted with water, acidified with dilute hydrochloric acid and the resultant precipitate is filtered and washed with water. It is purified using dimethylformamide (DMF) and water to form crystals.

Obtained: 22.1 g. Formula: $C_{15}H_{11}N_9O$. Yield: 83%.

TLC on silica gel (methylethylketone acetic acid - MeOH:8/0.3/1):Rf0.43

Melting point: 287° C.

Example 4

N-[4-(1H-tetrazol-5-yl)-pyridine-2-yl]-3-(1H-tetrazol-5-yl)benzamide (compound 4)

21g (0.32 moles) sodium azide and 18.7 g (0.35 moles) ammonium chloride are added to a suspension of 19.9 g (0.08 moles) N-[(4-cyano)-pyridine-2-yl]-

3-cyanobenzamide (compound 2) in 300 ml of DMF. The process is continued as in example 3.

Obtained: 19.5 g. Formula: $C_{14}H_{10}N_{10}O$. Yield: 73%.

TLC on silica gel (methylethylketone acetic acid

MeOH: 8/0.3/1): Rf 0.20

Melting point: 273°C.

All the compounds of formula I illustrated in the general synthesis diagram are synthesised by means of these processes. The chemico-physical properties of some of the compounds to which the invention relates are shown in Table 1.

Table 1: Chemico-physical properties of the compounds represented by formula I (diagram 1)

Compound	R ₁	A	R ₂	Melting point °C	Formula
3	3-trz ^a	phenyl	4-trz	287	$C_{15}H_{11}N_9O$
4	3-trz	pyridine-2-yl	4-trz	273	$C_{14}H_{10}N_{10}O$
5	4-trz	pyridine-2-yl	5-trz	266	$C_{14}H_{10}N_{10}O$
6	3-trz	phenyl	2-trz	227	$C_{15}H_{11}N_9O$
7	3-trz	phenyl	3-trz	290	$C_{15}H_{11}N_9O$
8	4-trz	phenyl	2-trz	256	$C_{15}H_{11}N_9O$
9	4-trz	phenyl	3-trz	283	$C_{15}H_{11}N_9O$
10	2-trz	phenyl	4-trz	261	$C_{15}H_{11}N_9O$

^a: trz: 1H-tetrazol-5-yl

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Of the pharmaceutically acceptable salts falling within the scope of the invention, sodium salt, ammonium salt, zinc salt, lysine salt and arginine salt are preferred.

As indicated above, the compounds to which the invention relates have remarkable pharmacological activity in mammals.

a) Anti-allergic activity

Certain of the compounds claimed have been shown to have a powerful anti-allergic activity. For example, these compounds prevent the development of a cutaneous anaphylactic reaction induced passively in rats by the antiserum IgE.

The process consists of a modification of the Goose and Blair method (Immunology 16 (1969, 749-760). Male rats weighing approximately 250g are treated intra-muscularly with 25 mg/kg of grade V ovalbumin dissolved in 0.5 ml of a Bordetella Pertussis suspension. 14 days later, after sensibilization, the animals are sacrificed by being anaesthetized with ether, the blood being sampled and the serum maintained at -70° C after the titre has been tested for IgE specific to the ovalbumin present therein. On the basis of the titre, in less than 24 hours, 2 intradermal injections of 0.1 ml of the titrated

antiserum in question, suitably diluted, are injected into the shaved back of male rats weighing approximately 200 g. At 0 time, 5 ml/kg of physiological solution containing 25 mg/kg antigen (ovalbumin) and 3 mg/kg Evans blue are injected intravenously.

The products in question are administered intramuscularly 15 minutes before the antigen. The animals are sacrificed 30 minutes after the antigen has been administered, the skin from the back is inverted and the maximum and minimum diameters of each spot are measured. In practice the response from each animal can be evaluated as a mean value of the four diameters. The compounds are administered in different doses (generally 5 animals per dose per group) such that it is possible to calculate an active 50 dose (ID50), the dose which can inhibit 50% of the passive cutaneous anaphylactic (PCA) reactions in the animals treated in accordance with the tests.

The results obtained in this way using the compounds described in Table 1 are given in Table 2.

Table 2: Effects on cutaneous anaphylaxis in rats passively sensitized (PCA) with antiserum IgE and the antigen ovalbumin

Compounds	ID ₅₀ ^a mg/kg
3	0.05(0.02-0.16)
4	0.24(0.08-0.73)
5	1.0 (0.19-5.3)
6	1.4 (0.6-2.9)
7	1.6 (0.9-3.0)
8	1.5 (0.4-6.1)
9	0.03(0.008-0.12)
10	1.8 (0.5-6.5)
DSCG ^b	1.5 (1.0-2.2)

^aID₅₀: is the dose in mg/kg of product (in brackets the fiducial limits when p=0.05) required to inhibit by 50% the anaphylactic reaction induced by 25 mg/kg of ovalbumin given intravenously.

^b : DSCG= disodium chromoglycate

From the results obtained it can be seen that the more active compounds according to the invention have an anti-allergic activity in the PCA test which is 30 -50 times greater than that of the DSCG taken as the reference remedy. Unexpectedly, only compounds 3 and 9 proved to be extremely potent, that is to say the compounds in which A is phenyl and R₁ and R₂ are the group (1H-tetrazol-5-yl) located in positions 3,4 or 4,3 alternately. In fact all the other compounds studied, with the exception of compound 4 which is also substantially potent, display anti-allergic activity in the PCA test which is comparable to that of DSCG.

b) Cytoprotective activity

The protective activity with respect to mucose membranes is assessed in a test ulcer induced by administering alcohol orally to rats. It has recently been reported that the antiallergic medicament sodium chromoglycate (DSCG) appears to be effective in the prevention of ethanol-induced gastric mucosal necrosis (J. Goossens et al. Br.J.Pharmacol. 91 (1987), 165-169).

The following procedure is used: 1.5 ml/animal of pure ethanol is administered orally to male rats weighing approximately 150 g which were starved for 24 hours. The compounds in question are

administered intravenously 15 minutes prior to the irritant.

One hour after the alcohol is administered, the animals are sacrificed, the stomach removed, opened by being cut along the long curvature and examined under the microscope (enlarged ten times) to find any necrotic lesions, which are counted and classified according to the method described herebelow which is a variant of the method described in Med. Exp. 4,284-292 (1961), consisting in allocating arbitrary points according to the number and severity of the lesions, according to the following criteria:

- 1 if the length of the necrotic area is < 2 mm
- 2 if the length of the necrotic area is between 2 and 4 mm
- 3 if the length of the necrotic area is > 4 mm
- 5 if the length of the necrotic area is > 4 mm and has a perforated ulcer.

An index of the lesions is thus obtained which is the total number of lesions multiplied by their relative points.

The compounds are administered intravenously in various doses such that a protective ID50 dose can

be calculated, that is the dose (given intravenously in mg/kg) which can inhibit 50% of gastric mucosal damage induced by the harmful agent. The results obtained in this way with some of the compounds to which the invention relates are given in table 3.

Table 3: Cytoprotective activity in ulcers caused by alcohol in rats

Compounds	ID ₅₀ ^a mg/kg IV
3	0.6 (0.2-2.1)
4	2.8 (1.0-7.8)
5	3.1 (1.2-8.2)
6	9.7 (6.2-15.2)
7	15.8(6.9-36.3)
8	6.1 (3.6-10.4)
9	1.1 (0.4-2.7)
10	10.8(4.5-25.8)
DSCG	50.8(20.3-127.2)
CIMETIDINE	IN ^b

^aID₅₀: is the intravenous dose in mg/kg of product (in brackets the fiducial limits when p=0.05) required to inhibit 50% of the ulcerogenic effect induced by the oral administration of 1.5 ml/animal of pure ethanol.

^b: IN, inactive at 50 mg/kg.

From the results given in the Table it can be seen that compounds 3 to 9 have a very potent cytoprotective activity of between 0.6 and 1.1 mg/kg given intravenously. The other compounds to which the invention relates are generally less active, although for some the activity is remarkable (<10 mg/kg). Of the components studied, DSCG proves to have poor activity and is approximately 50-100 times less active than the most potent compounds to which the invention relates, whilst the anti-ulcer medicament, cimetidine, remains completely inactive in this test.

c) Antisecretion activity

The antisecretion activity is determined in rats, using male animals weighing approximately 200 g and anaesthetised with urethane. Gastric secretion is stimulated using pentagastrine, histamine and carbachol. The slightly modified method of K.S. Lai (Gut 5 (1964), 327-341) is used.

After a tracheotomy, the oesophagus and duodenum are intubated. Perfusion is performed using a tepid solution (37°) of physiological solution which has been passed through the stomach by means of a peristaltic pump at a constant rate of 1 ml/minute. After stabilising for 20 minutes, perfusion with the stimulant dissolved in physiological solution is

performed for 120 minutes in the dose indicated in Table 4 at a rate of 0.95 ml/hour. After 60 minutes' perfusion (basal stimulation), the product in question is administered intravenously in a bolus and perfusion of the stimulant is continued for a further 60 minutes. The acid secretion is continuously recorded as a function of the time.

The activity of the product is evaluated as a percentage of the reduction in the acidity secreted after the product has been administered compared with the basal acidity measured during the first 60 minutes' collection time in which only the stimulant was present.

The antagonistic compounds tested are administered in different doses such that it is possible to calculate an ID50 which is the dose (given intravenously in mg/kg) which can inhibit up to 50% of the effect of the various agents stimulating the secretion in question.

The results obtained in this way are illustrated in Table 4 showing the activities of the compounds expressed as ID50 in the three different situations discussed, that is under the stimulus of pentagastrine, histamine and carbachol in the doses indicated in the table.

Table 4: Antagonistic activity (ID₅₀ mg/kg given intravenously) compared with gastric acid secretions induced by different agents in rats

Compound	ID ₅₀ mg/kg ^a		
	Pentagastrine (30 mcg/kg/h)	Histamine (2.8 mg/kg/h)	Carbachol (30 mcg/kg/h)
3	9.8	12.0	10.8
4	30.5	18.8	44.5
5	53.5	40.4	66.3
6	30.8	37.9	38.9
7	45.2	45.8	42.2
8	20.8	37.0	34.8
9	16.0	14.5	16.2
10	68.1	57.5	68.5
DSCG	(19%) ^b	NT ^c	NT

^a ID₅₀: is the intravenous dose in mg/kg of product required to inhibit by 50% the acid secretion induced by different agents in the dose indicated and administered by intravenous infusion.

^b: DSCG at 100 mg/kg inhibits 19% of gastric secretion (± 12 ; n=6)

^c: NT: not tested

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The antisecretion activity displayed by the compounds claimed against various stimulants is also highly potent. This is the case in particular for compounds 3 and 9, that is to say the compounds in which the tetrazol substituent is located alternately in position 3 or 4 of the two phenyl groups of the benzamide represented in the general formula. In this case the most active compound is compound 3 which exhibits an antisecretion ID50 of approximately 10 mg/kg in each of the test conditions studied, in which the gastric secretion of pentagastrine, histamine and carbachol is stimulated. Among the compounds claimed the least advantageous appear to be those in which tetrazol R₁ is in the ortho position (for example compound 10). DSCG is used as the comparison compound since the literature shows (A.K. Nicol et al., J. Pharm. Pharmacol. 1981, 33, 554-556) that it inhibits the acid secretion stimulated by pentagastrine. Under the test conditions using a stimulant concentration 10 times greater than that used in the cited method, the effect of DSCG is relatively modest, reducing the stimulated secretion of pentagastrine by only 19%, in the very high intravenous dose of 100 mg/kg.

The test data given above show the manner in which the compounds to which the invention relates have a remarkable antiallergic, antisecretion and

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cytoprotective activity. Some of the compounds claimed, for example compounds 3 and 9, have an antianaphylactic activity in vivo in the PCA test which is approximately 40 times greater than the compound DSCG, which is a recognized reference standard in the scientific literature. Furthermore these compounds also have a strong cytoprotective effect which is approximately 50 times greater than DSCG in the case of the more active compounds which enables damage to the epithelial membranes in contact with harmful agents to be prevented.

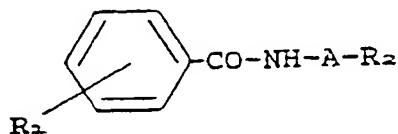
In view of this activity, as explained above, i.e. the cytoprotective and antiallergic effect, the favourable use of the compounds to which the invention relates in the treatment of all pathological conditions supported by allergic components such as for example bronchial asthma or rhinitis or allergic conjunctivitis is recommended. In pathological conditions of this type the compounds in question can act on the mastocytes in the form of a mechanism which is similar to a cytoprotective mechanism by stabilizing the cellular membranes, which would inhibit the release of chemical agents causing bronchospastic reactions in the lungs and inflammation of the mucosae.

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Furthermore, the above test data also show that the compounds to which the invention relates can be considered as a remarkable therapeutic innovation in the treatment of some pathological conditions of the gastro-duodenal tract, such as for example gastric and duodenal ulcers, ulcerative colitis, etc. In addition to a strong cytoprotective activity, these compounds display notable antagonistic activity with respect to gastric acid secretion induced by various stimulants such as pentagastrine, histamine and carbachol. Their anti-ulcer activity thus appears to be explained by a dual protective mechanism which inhibits both an excess formation of gastric acid stimulated by various agents and protects the mucose membranes from harmful agents. Furthermore, these compounds can also be used to prevent or cure lesions to any tissue exposed to harmful pathogens which damage the integrity thereof.

CLAIMS

1. Pharmaceutically active N-phenyl-benzamide and N-pyridinyl-benzamide compounds having the formula (I)



in which A is the benzene ring or the pyridine ring and R_1 and R_2 are both the group (1H tetrazol-5-yl) and in which, if R_1 is in the ortho or meta position in the benzamide group, R_2 is in the ortho, meta or para position in ring A, whereas if R_1 is in the para position in the benzamide group, R_2 can be in the ortho or meta position in ring A, and their pharmaceutically acceptable salts.

2. N-phenyl-benzamide compounds according to Claim 1, of formula (I), in which A is the benzene ring and R_1 and R_2 have the meanings given in Claim 1.

3. An N-pyridinyl-benzamide compound according to Claim 1, of formula (I), in which A is the pyridine ring and R_1 and R_2 have the meanings given in Claim 1.

4. A compound derived from N-phenyl-benzamide according to Claim 1, of formula (I), in which R_1 is the group 3-(1H-tetrazol-5-yl), A is the phenyl group and R_2 is the group 4-(1H-tetrazol-5-yl).

5. A compound derived from B-phenyl-benzamide according to Claim 1, of formula (I), in which R_1 is the group 4-(1H-tetrazol-5-yl), A is the phenyl group and R_2 is the group 3-(1H-tetrazol-5-yl).

6. A compound derived from N-pyridinyl-benzamide according to claim 1, of formula (I), in which R_1 is the group 3-(1H-tetrazol-5-yl), A is the pyridine (2-yl) group and R_2 is the group 4-(1H-tetrazol-5-yl).

7. Pharmaceutical compositions comprising a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

8. Pharmaceutical compositions according to Claim 7 for use in the therapeutic treatment of pathological conditions of the respiratory system connected with allergic phenomena such as allergic rhinitis and bronchial asthma, or in the therapy of irritating conditions of the eye, such as allergic conjunctivitis.

9. Pharmaceutical compositions according to Claim 7 for use in the therapeutic treatment of pathological conditions of the gastro-intestinal tract such as gastritis, duodenitis, gastric ulcers, duodenal ulcers, ulcerative colitis, and in alimentary allergies and intolerance as well as their use in preventing or curing lesions of any tissue exposed to harmful pathogens impairing the integrity thereof.

10. Pharmaceutical compositions according to Claim 7 in the use of therapeutic treatments of all systemic pathological manifestations, or those localized in various organs or apparatus, of an immunological origin (deriving from Ag-AC reactions or immunological response agents).

11. A process for preparing N-phenyl-benzamide derivatives and N-pyridinyl-benzamide derivatives of formula (I) in which A, R₁ and R₂ have the meanings given above, and their pharmaceutically acceptable salts, characterized in that it comprises the operations of: reacting aniline or aminopyridine advantageously substituted in R₂ with the cyano group with a stoichiometric amount of benzoyl chloride advantageously substituted in R₁ with the cyano group, dissolved in a polar solvent, in the presence of a tertiary base,

at a temperature of between 0 and 20°, for an amount of time which can vary from approximately one hour to 24 hours, and recovering the intermediate compounds (marked "W" in the general synthesis diagram) from the reactive mass, and purifying them optionally by means of crystallization; then reacting the compounds obtained in this manner in the hot state with sodium azide and ammonium chloride in a molar ratio of 1 : 5, in a high-boiling point solvent at a temperature of between 60° C and 140° C, giving bis-tetrazol compounds of formula (I) which are recovered from the reactive mass by acidification and purification by means of crystallization.

12. A process according to Claim 11, wherein said tertiary base is triethylamine.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/00326

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5	C07D257/04;	C07D401/14; A61K31/41; A61K31/44
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO,A,9 009 989 (ROTTA RESEARCH LABORATORIUM S.P.A.) 7 September 1990 see pages 8,9 (example 13) and claims ---	1-12
A	WO,A,8 605 779 (YAMANOUCHI PHARMACEUTICAL CO. LTD.) 9 October 1986 see pages 51-54 (examples 20-23) and claims ---	1,7-12
A	EP,A,0 286 364 (RIKER LABORATORIES, INC.) 12 October 1988 see claims -----	1,7-12
<p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
04 MAY 1993		14. 05. 93
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		CHOULY J.

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